Remarks

The Examiner has provided two rejections that are addressed in the following order:

I. Claims 1 and 3-7 are rejected under 35 USC § 112 ¶ 1 as allegedly not enabled.

II. Claims 1 and 3-7 are rejected under 35 USC § 103(a) as allegedly being unpatentable over United States Patent No. 4,748,018, in view of Uemura et al., as evidenced by Merck Manual.

I. The Claims Are Enabled

The Examiner argues:

> There is insufficient guidance in the specification as filed as to how the skilled artisan would make and use the *Clostridium perfringens* antibody in prophylactic purpose without undue experimentation.

Office Action pg 3 ¶ 2. Applicants disagree. First, since the Examiner admits that therapeutic treatment is enabled, the Examiner must articulate reasons why using the very same antibodies shown useful in therapeutic administrations (where the infection has already taken hold) would not be useful in advance of infection. The Examiner has provided no such reasons. Furthermore, since Claim 7 is limited to therapeutic administration, it should not be rejected.

With regard to "how the skilled artisan would make . . . the *Clostridium perfringens* antibody" the specification is quite clear and provides ample guidance. For example, Table 1 on page 8 provides the specific toxins for *C. perfringens* in the context of using them as immunogens. Under Table 1, the text goes on to note that "When immunization is used, the preferred non-mammal is from the class Aves . . . [and that] A preferred bird is a chicken." (page 8, lines 15-18). On the next page, the specification teaches how to obtain antibodies from the egg yolk (page 9). The specification also

teaches how the toxins can be modified to reduce toxicity but preserve immunogenicity (page 9, lines 20-30).

The specification also teaches that immunization can be done with adjuvants (page 10). In addition, the specification provides guidance on what kind of immunization schedule should be used in order to raise strong anti-Clostridium antibodies, with a suggestion that the collection time be "after day 100." (page 10, line 23). Furthermore, detailed guidance is provided with regard to extraction and purification (page 11). Finally, actual examples where Clostridial toxins are used to generate antibodies are provided.

Thus, with respect to teaching "how the skilled artisan would make" the antibodies, the Examiner's position is simply untenable. The specification provides the requisite teachings to enable one skilled in the art to raise antibodies to Clostridial toxins, including the toxins of *C. perfringens*.

Turning now to the question of "how to use" the antibodies prophylactically, Applicants submit the specification provides specific guidance. First, the specification teaches that the "preferred method of treatment is by *oral administration* of antitoxin." (page 11, lines 28-30, emphasis added). With respect to dosage, the specification provides specific teaching that the use of "PEG-purified antitoxin from birds" permits more flexibility in dosage because of the reduction in total protein and because bird antibody does not fix complement (page 12, lines 20-27). With respect to prophylactic use the specification is quite clear:

> "The invention also contemplates a method of treatment which can be administered prophylactically. In one embodiment, antitoxin is administered orally, in a delivery solution, in therapeutic dosage, to a subject, to prevent intoxication of the subject by the bacterial toxin which served as immunogen for the antitoxin."

(Page 13, lines 17-22). Thus, use of one or more of the *C. perfringens* toxins of Table 1 can be used to make antibody, which can be used to prevent intoxication by the toxin used as the immunogen.

To address the Examiner's assertion of "unpredictability of the art," a declaration is provided which points to experiments done by the same group of applicants in a related patent application (now issued) which demonstrate PREVENTION against *C. difficile*

toxins by prophylactic administration of antibody (see attached Declaration of Dr. Stafford, paragraph 3). This data shows that the teachings in the present specification reliably generate "antibodies to a Clostridial toxin [that] can be readily used prophylactically where (as with *C. perfringens*) the toxins are not automatically lethal." (see Declaration, paragraph 3).

The teachings of the present specification, together with the data and statements in the Declaration, show that the Examiner's position with regard to enablement is unfounded. It is respectfully requested that the rejection be withdrawn.

II. The Claims Are Not *Prima Facie* Obvious

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A Prima Facie Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants submit that the Examiner's rejection does not meet these criteria. The Applicants rebut the establishment of a *prima facie* case of obviousness by the argument below.

A. The 018 Patent Does Not Teach *C. perfringens* and Requires Further Steps In Order to Induce Tolerance

The Examiner acknowledges that the 018 Patent does not teach anything about *C. perfringens*. However, the Examiner fails to note that the 018 Patent requires that the mammal being tolerant to the antibody by virtue of having a history of consumption of antibody . This makes the teachings of the 018 Patent impractical (see Declaration of Dr. Stafford, paragraph 4) and undermines any notion that such teachings can be readily combined with anything else.

Indeed, the 018 teaches that the use of heterologous antibodies cannot otherwise be done safely:

> The failure of the immune system of an animal to respond to foreign protein is a condition known as immunological tolerance. Moreover, it is well known to those skilled in the art of immunology that mammals of a given species lack tolerance to antibodies from various animal species, including other mammalian species. *It is therefore apparent that heterologous antibodies obtained from alien species cannot be safely used to treat mammals*

(see the 018 Patent, DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS, first paragraph). This is an explicit statement in the cited art that indicates there is NO chance of success without tolerance. This teaches away from the presently claimed invention.

B. Uemura et al. Provides No Teachings Regarding Therapy

The Examiner argues that "it would have been obvious . . . to employ *Clostridium perfringens* . . . as taught by Uemura et al into the therapeutic method . . . as taught by the 018 patent." *Office Action, page 4.* However, the Uemura et al. publication does not deal with therapy. As noted by Dr. Stafford, the paper provides no direct connection between serum antibody and exposure, and offers no insight or suggestion on the existence, role in disease resistance, or medicament value of luminal toxin antibodies (or any antibodies for that matter) in *C. prefringens* disease. (Declaration, paragraph 5). Accordingly, there is no basis for combining the references or asserting "it would be obvious."

The Applicants, therefore, respectfully request that the Examiner withdraw the present rejection.

C. Further Evidence Of Non-obviousness

The Examiner provides some 2004 paperwork from the Arizona Department of Health concerning *C. perfringens*. However, under the section "Prophylactic Treatment" there is absolutely no discussion of antibodies. This is further evidence that even those skilled in the health field are unaware of the preventative value of oral antibodies in this context.

CONCLUSION

Applicants believe that the arguments set forth above traverse the Examiner's rejections and, therefore, request that these grounds for rejections be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

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